PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P11067 PC	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/012060	International filing date *(day/month/year)* 21.10.2004	Priority date *(day/month/year)* 22.10.2003
International Patent Classification (IPC) or national classification and IPC A61K9/26, A61K31/167, A61P35/00, A61K9/16		
Applicant LIDDS AB		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.08.2005	27.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Albrecht, S Telephone No. +49 89 2399-7864

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/012060

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-27	as originally filed
Claims, Numbers	
1-64	received on 23.12.2005 with letter of 21.12.2005
Drawings, Sheets	
1/2, 2/2	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 65-72
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/012060

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 33-36

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 33-36 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos:

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32,37-64
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32,37-64
Industrial applicability (IA)	Yes:	Claims	1-64
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I
Basis of the report

With his letter of 21-12-2005, the applicant has filed a new set of claims 1-64. These modifications do not introduce subject-matter which extends beyond the content of the original application, and thus fulfill the requirements of Art.34(2)(b) PCT.

Re Item II
Priority

The claimed priority dates of documents SE0302782-8 (22/10/2003) and US60/561875 (14/04/2004) appear to be invalid for the present application, since neither gas-forming agents nor pore-sealing agents are mentioned in these documents.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Claims 33-36 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved. Such a definition is only allowable under the conditions elaborated in the PCT Preliminary examination Guidelines, chapter 5.35. In this instance, however, such a formulation is not acceptable because the result cannot be achieved without undue in vivo experimentation.

Accordingly, novelty and inventive step issues cannot be discussed for these claims.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D1-D8) are referred to in this report; the numbering results from the order of citations found in the Search Report (SR) and will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise

specified.

V.1. Novelty

V.1.1. Claims 1-32, 37-64 appear to be novel over the available prior art.

V.2. Inventive step

a) D1, which is considered to represent the most relevant state of the art, discloses in example 15 a pharmaceutical composition comprising biodegradable hydrating ceramics (calcium dihydrogenophosphate, calcium sulfate), a gas forming agent (sodium bicarbonate), a pore-sealing agent (dextran), a sorbed aqueous medium and optionally an active agent (amikacin sulfate). Said composition enables a sustained release of the active agent.

b) The subject-matter of claims 1-64 differs from D1 in that the concentration of the in D1 used gas-forming agent is above 1% w/w (approx. 1,55% w/w).

c) Starting from D1, the technical problem to be solved by the present invention can be defined as finding a drug carrier composition providing a sustained release of an active agent, which exhibits an improved mechanical strength after solidification.

d) The solution proposed by the applicant constitutes a composition as defined in independent claims 1, 41, 62, 63.

e) However, present claims 1-64 cannot be regarded as inventive in the sense of Article 33(3) PCT, the reasons being as follows:

According to the Applicant's opinion stated in his letter of 21-12-2005, compositions according to example 15 of D1 containing 3,03% w/w and 1,58% w/w of sodium bicarbonate respectively ("composition I" and "composition II"), are not suitable for the use according to the present invention, namely a sustained local release of an active agent over a prolonged period of time, as their mechanical strength after solidification is insufficient. Furthermore, composition I is not able to cure.

Nevertheless, as the scope of independent claims 1, 41, 62, 63 also encompasses compositions which are not in solid form (cfr. claims 13, 14), and such compositions are referred to in the description of the present application as being equally suitable for the use according to the invention (cfr. p.4, l.33 - p.5, l.4; p.5, l.31-35), the characteristics of reasonable curing time and sufficient mechanical strength after solidification outside the patient's body can only be taken into account for those compositions which solidify before being administered to the patient. However, for those compositions the applicant does not provide any evidence in form of experimental data which substantiates the alleged effect (sufficient mechanical strength) of said distinguishing feature of the concentration of the gas-forming agent. Therefore, at present no unexpected or surprising effect can be attributed to said feature with respect to those compositions which solidify outside the patient's body. The same applies to the compositions which begin to solidify in vivo only. In the absence of such an effect, the selection of the claimed concentration range has to be considered as being an arbitrary selection carried out without applying inventive skill.

Claims

1. A pharmaceutical composition comprising
i) one or more biodegradable hydrating ceramics
ii) one or more gas forming agents in a concentration of from about 0.1% to about 1% w/w,
iii) sorbed aqueous medium,
iv) one or more therapeutically, prophylactically and/or diagnostically active substances, and
v) one or more pore-sealing agents,
which in solid form has a ruptured structure.

2. A pharmaceutical composition according to claim 1, which in solid form has a foam-like structure with openings, wherein at least 50% or more have a largest width of at least about 0.1 mm.

3. A pharmaceutical composition according to claim 1, wherein, in solid form, has at least 60% such as, e.g., at least 70%, at least 75%, at least 80%, at least 85% or at least 90% of the openings have a largest width of at least about 0.1 mm.

4. A pharmaceutical composition according to any of the preceding claims, wherein the openings have a largest width of at least about 0.2 mm such as, e.g. at least about 0.3 mm, at least about 0.4 mm, at least about 0.5 mm.

5. A pharmaceutical composition according to any of the preceding claims, wherein the openings have a largest width of at least about 0.6 mm such as, e.g. at least about 0.8 mm, at least about 1.0 mm, or from about 0.1 mm to about 2 mm such as, e.g., from about 0.3 mm to about 1.5 mm or from about 0.5 mm to about 1.5 mm.

6. A pharmaceutical composition according to claim 1, wherein the surface area of an opening in cross sectional view having a largest width of at least about 0.1 mm is at least about 3×10^{-8} m^2 such as, e.g. at least about 5×10^{-8} m^2, at least 1×10^{-7} m^2, at least about 5×10^{-7} m^2, at least about 1×10^{-6} m^2, or about 5×10^{-6} m^2 or more.

7. A pharmaceutical composition according to any of the preceding claims, wherein the biodegradable hydrating ceramic is selected from the group consisting of non-hydrated or hydrated calcium sulphate, calcium phosphate, calcium carbonate, calcium fluoride,

calcium silicate, magnesium sulphate, magnesium phosphate, magnesium carbonate, magnesium fluoride, magnesium silicate, barium sulphate, barium phosphate, barium carbonate, barium fluoride, barium silicate, or mixtures thereof.

8. A pharmaceutical composition according to any of the preceding claims, wherein the biodegradable hydrating ceramic is non-hydrated or hydrated calcium sulphate.

9. A pharmaceutical composition according to any of the preceding claims, wherein the biodegradable hydrating ceramic employed in the preparation of the composition is in the form of a powder.

10. A pharmaceutical composition according to claim 9, wherein the powder has a mean particle size of at the most about 75 μm such as, e.g., at the most about 50 μm, at the most about 25 μm or at the most about 10 μm.

11. A pharmaceutical composition according to any of the preceding claims, wherein the gas-forming agent is, e.g., alkali metal carbonates including sodium carbonate and potassium carbonates; alkali metal hydrogen carbonates including sodium hydrogen carbonate and potassium hydrogen carbonate; and hydrogen peroxide.

12. A pharmaceutical composition according to any of the preceding claims, wherein the concentration of sorbed aqueous medium is at the most about 60% w/w such as, e.g., at the most about 50% w/w, at the most about 45% w/w, at the most about 40% w/w or at the most about 30% w/w of the total composition.

13. A pharmaceutical composition according to any of the preceding claims in liquid, semi-solid or solid form.

14. A pharmaceutical composition according to claim 13 in the form of a paste or another semi-solid form.

15. A pharmaceutical composition according to any of the preceding claims having a shape like e.g. beads, pellets, tubes, polygons, spheres, stars, cubes, etc.

16. A pharmaceutical composition according to any of the preceding claims, wherein the therapeutically, prophylactically and/or diagnostically active substance is an anti-cancer agent.

17. A pharmaceutical composition according to claim 16, wherein the anti-cancer agent is an androgen or a derivative thereof, an anti-androgen or a derivative thereof, an oestrogen or a derivative thereof, an anti-oestrogen or a derivative thereof, a gestagen or a derivative thereof, an anti-gestagen or a derivative thereof, an oligonucleotide, a progestagen or a derivative thereof, a gonadotropin-releasing hormone or an analogeu or derivative thereof, a gonadotropin inhibitor or a derivative thereof, an adrenal and/or prostate enzyme inhibitor, a membrane efflux and/or membrane transport protein, an immune system modulator, an angiogenesis inhibitor, or combinations thereof.

18. A pharmaceutical composition according to claim 17, wherein the anti-androgen is flutamide, hydroxy-flutamide, cyproteron, nilutamide or bicalutamide or the like.

19. A pharmaceutical composition according to claim 16, wherein the anti-cancer agent is a combination of an anti-androgen and a gonadotropin-releasing hormone or an analogue thereof.

20. A pharmaceutical composition according to any of the preceding claims, wherein the active substance is homogeneously dispersed in the biodegradable hydrating ceramic.

21. A pharmaceutical composition according to any of the preceding claims for parenteral use.

22. A pharmaceutical composition according to any of the preceding claims, wherein the one or more biodegradable hydrating ceramics, the gas forming agent and the one or more active substance are homogeneously dispersed in water so that the hydrating ceramic, the gas forming agent and/or the active substance sorbs water.

23. A pharmaceutical composition according to any of the preceding claims, which solidifies after a suitable time period of about 20 min or less such as, e.g. about 15 min or less, about 10 min or less or about 5 min or less when stored at 37°C.

24. A pharmaceutical composition according to any of the preceding claims, wherein the one or more biodegradable hydrating ceramics have a microporous structure.

25. A pharmaceutical composition according to claim 24, wherein at least part of the microporous structures is sealed with a pore-sealing agent.

26. A pharmaceutical composition according to claim 24 or 25, wherein at least 50% such as, e.g., 60% or more, 70% or more, 80% or more or 90% or more of the microporous structures is sealed with a pore-sealing agent.

27. A pharmaceutical composition according to claim 25 or 26, wherein the pore-sealing agent is a hydrophobic agent, a hydrophilic agent or a water-absorbing agent.

28. A pharmaceutical composition according to claim 27, wherein the hydrophobic agent is selected from the group consisting of silicone oil, silicon rubber, waxes, paraffinic hydrocarbons, polyvinylalcohols and ethyl cellulose.

29. A pharmaceutical composition according to claim 27, wherein the hydrophilic agent is selected from the group consisting of methylcellulose, hyaluronic acid, dextran and poly-ethylene glycol (PEG).

30. A pharmaceutical composition according to claim 27, wherein the water-absorbing agent is selected from the group consisting of water glasses, silica gel and sodium phosphate.

31. A pharmaceutical composition according to any of claims 25-30, wherein the concentration of the pore-sealing agent in the composition is about 30% w/w or less such as, e.g., about 25% w/w or less or about 20% or less in the final composition.

32. A pharmaceutical composition according to any of the preceding claims, wherein the active substance is controlled released from the composition.

33. A pharmaceutical composition according to claim 32, wherein at the most about 10% w/w of the active substance contained in the composition is released 5 days or more after implantation to a human.

34. A pharmaceutical composition according to claim 32 or 33, wherein at the most about 50% w/w of the active substance contained in the composition is released 1 month or more after implantation to a human.

35. A pharmaceutical composition according to any of claims 32-34, wherein at the most about 75% w/w of the active substance contained in the composition is released 1.5 month or more such as, e.g., 2 month or more after implantation to a human.

36. A pharmaceutical composition according to any of claims 32-35, wherein at the most about 100% w/w of the active substance contained in the composition is released 2 month or more such as 2.5 month or more or 3 month or more after implantation to a human.

37. A pharmaceutical composition according to claim 32, wherein at the most about 10% w/w of the active substance contained in the composition is released after 2 days or more – when tested in an *in vitro* dissolution test according to Ph.Eur. (paddle).

38. A pharmaceutical composition according to claim 32 or 37, wherein at the most about 50% w/w of the active substance contained in the composition is released after 1 month or more – when tested in an *in vitro* dissolution test according to Ph.Eur. (paddle).

39. A pharmaceutical composition according to any of claims 32, 37-38, wherein at the most about 75% w/w of the active substance contained in the composition is released after 1.5 month or more such as, e.g., 2 month or more – when tested in an *in vitro* dissolution test according to Ph.Eur. (paddle).

40. A pharmaceutical composition according to any of claims 32, 37-39, wherein at the most about 100% w/w of the active substance contained in the composition is released after 2 month or more such as 2.5 month or more or 3 month or more – when tested in an in vitro dissolution test according to Ph.Eur. (paddle).

41. A drug carrier composition comprising

i) one or more biodegradable hydrating ceramics

ii) one or more gas forming agents in a concentration of from about 0.1% to about 1% w/w, and

iii) sorbed aqueous medium
which in solid form has a ruptured structure, wherein at least part of the micro-porous structure is sealed with a pore-sealing agent.

42. A drug carrier composition according to claim 41, which in solid form has a foam-like structure with openings, wherein at least 50% or more have a largest width of at least about 0.1 mm.

43. A drug carrier composition according to claim 42, wherein, in solid form, at least 60% such as, e.g., at least 70%, at least 75%, at least 80%, at least 85% or at least 90% of the openings have a largest width of at least about 0.1 mm.

44. A drug carrier composition according to any of claims 42-43, wherein the openings have a largest width of at least about 0.2 mm such as, e.g. at least about 0.3 mm, at least about 0.4 mm, at least about 0.5 mm.

45. A drug carrier composition according to any of claims 42-44, wherein the openings have a largest width of at least about 0.6 mm such as, e.g. at least about 0.8 mm, at least about 1.0 mm, or from about 0.1 mm to about 2 mm such as, e.g., from about 0.3 mm to about 1.5 mm or from about 0.5 mm to about 1.5 mm.

46. A drug carrier composition according to any of claims 42-45, wherein the surface area of an opening in cross sectional view having a largest width of at least about 0.1 mm is at least about 3 $x10^{-8}$ m^2 such as, e.g. at least about 5 $x10^{-8}$ m^2, at least about 1 $x10^{-7}$ m^2, at least about 5 $x10^{-7}$ m^2, at least about 1 $x10^{-6}$ m^2, or about 5 $x10^{-6}$ m^2 or more.

47. A drug carrier composition according to claim 41, which in solid form has a ruptured structure obtained by disintegration into two or more parts.

48. A drug carrier composition according to claim 47, wherein the two or more parts have an external surface area that is at least about twice as large as that of the composition before disintegration such as, e.g. at least about ten times as large, at least about a hundred times as large, or about a thousand times as large or more.

49. A drug carrier composition according to any of claims 41-48, wherein the

biodegradable hydrating ceramic is selected from the group consisting of non-hydrated or hydrated calcium sulphate, calcium phosphate, calcium carbonate, calcium fluoride, calcium silicate, magnesium sulphate, magnesium phosphate, magnesium carbonate, magnesium fluoride, magnesium silicate, barium sulphate, barium phosphate, barium carbonate, barium fluoride, barium silicate, or mixtures thereof.

50. A drug carrier composition according to any of claims 41-49, wherein the biodegradable hydrating ceramic is non-hydrated or hydrated calcium sulphate.

51. A drug carrier composition according to any of claims 41-50, wherein the biodegradable hydrating ceramic employed in the preparation of the carrier composition is in the form of a powder.

52. A drug carrier composition according to claim 51, wherein the powder has a mean particle size of at the most about 75 μm such as, e.g., at the most about 50 μm, at the most about 25 μm or at the most about 10 μm.

53. A drug carrier composition according to any of claims 41-52, wherein the gas-forming agent is, e.g., alkali metal carbonates including sodium carbonate and potassium carbonates; alkali metal hydrogen carbonates including sodium hydrogen carbonate and potassium hydrogen carbonate; and hydrogen peroxide.

54. A drug carrier composition according to any of claims 41-53, wherein the concentration of sorbed aqueous medium is at the most about 60% w/w such as, e.g., at the most about 50% w/w, at the most about 45% w/w, at the most about 40% w/w or at the most about 30% w/w of the total composition.

55. A drug carrier composition according to any of claims 41-54 in liquid, semi-solid or solid form.

56. A drug carrier composition according to claim 55 in the form of a paste or another semi-solid form.

57. A drug carrier composition according to any of claims 41-56 having a shape like e.g. beads, pellets, tubes, polygons, spheres, stars, cubes, etc.

58. A drug carrier composition according to any of claims 41-57 further comprising one or more therapeutically, prophylactically and/or diagnostically active substances.

59. A drug carrier composition according to claim 58, wherein the active substance is homogeneously dispersed in the biodegradable hydrating ceramic.

60. A drug carrier composition according to any of claims 41-59, wherein the one or more biodegradable hydrating ceramics and the gas forming agent are homogeneously dispersed in water so that the hydrating ceramic and/or the gas forming agent sorbs water.

61. A drug carrier composition according to any of claims 41-60, which solidifies after a suitable time period of about 20 min or less such as, e.g. about 15 min or less, about 10 min or less or about 5 min or less when stored at 37°C.

62. A composition in particulate form for use in the preparation of a drug carrier composition as defined in any of claims 41-61 or a pharmaceutical composition as defined in any of claims 1-40, the composition comprising
i) one or more biodegradable hydrating ceramics in powder form
ii) one or more gas forming agents in a concentration of from about 0.1% to about 1% w/w,
iii) optionally, one or more therapeutically, prophylactically and/or diagnostically active substances, and
iv) one or more pore-sealing agents.

63. A method for the preparation of a pharmaceutical composition as defined in any of claims 1-40, which method comprises dispersing a mixture of
i) one or more biodegradable hydrating ceramics in powder form, and
ii) one or more gas forming agents in a concentration of from about 0.1% to about 1% w/w,
in
iii) an aqueous medium,
wherein either the mixture of i) and ii), or iii) further comprises
iv) one or more therapeutically, prophylactically and/or diagnostically active substances, and
v) one or more pore-sealing agents.

64. A method according to claim 63, wherein the pharmaceutical composition is an injectable and *in vivo* solidifying composition for controlled release of the active substance.